Chapter 42: Influenza

INTRODUCTION

- *Influenza* is a viral illness associated with high mortality and high hospitalization rates. The highest rates of severe illness, hospitalization, and death occur among those older than age 65 years, young children (younger than 2 years old), and those who have underlying medical conditions, including pregnancy and cardiopulmonary disorders.
- The route of influenza transmission is person-to-person via inhalation of respiratory droplets, which can occur when an infected person coughs or sneezes. The incubation period for influenza ranges between 1 and 7 days, with an average incubation of 2 days. Adults are considered infectious from the day before their symptoms begin through 7 days after the onset of illness, whereas children can be infectious for longer than 10 days after the onset of illness. Viral shedding can persist for weeks to months in severely immunocompromised people.

CLINICAL PRESENTATION

- The presentation of influenza is similar to a number of other respiratory illnesses.
- The clinical course and outcome are affected by age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, and the degree of preexisting immunity.
- Complications of influenza may include exacerbation of underlying comorbidities, primary viral pneumonia, secondary bacterial pneumonia or other respiratory illnesses (eg, sinusitis, bronchitis, and otitis), encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome.

Signs and Symptoms

- Classic signs and symptoms of influenza include rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.
- Nausea, vomiting, and otitis media are also commonly reported in children.
- Signs and symptoms typically resolve in 3–7 days, although cough and malaise may persist for more than 2 weeks.

Laboratory Tests

- The gold standard for diagnosis of influenza is reverse-transcription polymerase chain reaction (RT-PCR) or viral culture.
- Rapid influenza diagnostic tests (RIDTs), also known as point-of-care (POC) tests, direct (DFA) or indirect (IFA) fluorescence antibody tests, and the RT-PCR assay may be used for rapid detection of virus.
- Chest radiograph should be obtained if pneumonia is suspected.

PREVENTION

- The best means to decrease the morbidity and mortality associated with influenza is to prevent infection through vaccination. Appropriate infection control measures, such as hand hygiene, basic respiratory etiquette (cover your cough and throw tissues away), and contact avoidance, are also important in preventing the spread of influenza. Additionally, chemoprophylaxis is useful in certain situations.

- Annual vaccination is recommended for all persons age 6 months or older and caregivers (eg, parents, teachers, babysitters, nannies) of children less than 6 months of age.
- Vaccination is also recommended for those who live with and/or care for people who are at high risk, including household contacts and healthcare workers.
- The Advisory Committee on Immunization Practices (ACIP) has made the following recommendations regarding the vaccinations of persons with reports of egg allergy: (a) vaccination with any age appropriate IIV or RIV3 vaccine, for persons with a history of egg allergy that involves only hives; (b) Persons with severe allergic reactions (ie, symptoms other than hives), such as angioedema, respiratory distress, light-headedness, or recurrent emesis or required epinephrine after an egg exposure may be immunized with any licensed IIV or RIV3 that is appropriate for age and health status; (c) Severe allergic reaction to influenza vaccine is a contraindication to receiving future vaccinations; (d) Vaccine providers should consider observing all patients for 15 minutes after vaccination to decrease the risk for injury should a patient experiences syncope.

✔ The ideal time for vaccination is October or November to allow for the development and maintenance of immunity during the peak of the influenza season.

✔ The two vaccines currently available for prevention of influenza are the inactivated vaccine IIV and the LAIV. The specific strains included in the vaccine each year change based on antigenic drift.

✔ IIV is FDA approved for use in people over 6 months of age, regardless of their immune status. Several commercial products are available and are approved for different age groups (**Table 42-1**). Because the vaccine content can change each year, vaccination providers should consult the most recent recommendations of the ACIP regarding use of seasonal influenza vaccines in the United States.

✔ Adults older than 65 years benefit from influenza vaccination, including prevention of complications and decreased risk of influenza-related hospitalization and death. However, people in this population may not generate a strong antibody response to the vaccine and may remain susceptible to infection.

✔ The most frequent adverse effect associated with IIV is soreness at the injection site that lasts for less than 48 hours. IIV may cause fever and malaise in those who have not previously been exposed to the viral antigens in the vaccine. Allergic-type reactions (hives and systemic anaphylaxis) rarely occur after influenza vaccination and are likely a result of a reaction to residual egg protein in the vaccine.

✔ Vaccination should be avoided in persons who are not at high risk for influenza complications and who have experienced Guillain–Barré syndrome within 6 weeks of receiving a previous influenza vaccine.

✔ LAIV is made with live, attenuated viruses and is approved for intranasal administration in healthy people between 2 and 49 years of age (**Table 42-2**). Advantages of LAIV include its ease of administration, intranasal rather than intramuscular administration, and the potential induction of broad mucosal and systemic immune response.

✔ The adverse effects typically associated with LAIV administration include runny nose, congestion, sore throat, and headache.

✔ LAIV should not be given to immunosuppressed patients or given by healthcare workers who are severely immunocompromised. LAIV is not recommended in several populations, including people older than 50 years and pregnant women.

TABLE 42-1

Approved Influenza Vaccines for Different Age Groups—United States, 2019–2020 Season

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Thimerosal Mercury Content (mcg Hg/0.5-mL dose)	Age Group	Number of Doses
Trivalent IIV (IIV3s)—adjuvanted and high dose						
aIIV3	Fluad	Seqirus	0.5-mL single dose	0	≥65 years	1

			prefilled syringe			
IIV3 High dose	Fluzone HD	Sanofi Pasteur	0.5-mL prefilled syringe	0	≥65 years	1
Quadrivalent IIVs (IIV4s)						
IIV4	Afluria	Seqirus	0.25-mL prefilled syringe	0	6–35 months	1 or 2[a]
			0.5-mL prefilled syringe	0	≥3 years	1 or 2[a]
			5-mL multidose vial	24.5	≥6 months via needle/syringe or 18–64 years via jet injector	1 or 2[a]
IIV4	Fluarix Quadrivalent	GlaxoSmithKline	0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
IIV4	FluLaval Quadrivalent	GlaxoSmithKline	0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
			5-mL multidose vial	<25	≥6 months	
IIV4	Fluzone Quadrivalent[b]	Sanofi Pasteur	0.25-mL prefilled syringe	0	≥6–35 months	1 or 2[a]
			0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
			0.5-mL single-dose vial	0	≥6 months	1 or 2[a]
			5-mL multidose vial	25	≥6 months	1 or 2[a]
Quadrivalent IIV high dose (IIV4-HD)						
IIV4 High dose	Fluzone HD Quadrivalent	Sanofi Pasteur	0.7-mL prefilled syringe	0	≥65 years	1
Cell culture–based quadrivalent IIVs (ccIIV4)						
ccIIV4	Flucelvax Quadrivalent	Seqirus	0.5-mL prefilled syringe	0	≥4 years	1 or 2[a]
			5-mL multidose vial	25	≥4 years	1 or 2[a]
Recombinant quadrivalent IIVs (RIV4)						

RIV4	Flublok Quadrivalent	Sanofi Pasteur	0.5-mL prefilled syringe	0	≥18 years	1
LAIV quadrivalent (LAIV4)						
LAIV	FluMist Quadrivalent	AstraZeneca	0.2-mL sprayer	0	2–49 years	1 or 2[c]

[a]Two doses administered at least 4 weeks apart are recommended for children aged 6 months to less than 9 years who are receiving influenza vaccine for the first time or received one dose in first year of vaccination during the previous influenza season.

[b]Fluzone Quadrivalent may be given to children aged 6 through 35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or the other dose volume for this age group. Persons aged ≥3 years should receive 0.5-mL dose volume.

[c]Two doses administered.

IIV, inactivated influenza vaccine; IIV3, inactivated influenza trivalent vaccine; aIIV3, adjuvanted inactivated influenza vaccine, trivalent, standard dose; IIV4, inactivated influenza quadrivalent vaccine; IIV4-HD, inactivated influenza quadrivalent vaccine—high dose; ccIIV3, cell culture-based trivalent influenza vaccine; RIV4, recombinant quadrivalent influenza vaccine; LAIV, live-attenuated influenza vaccine.

Note: IIVs and RIV4 may be administered concomitantly or sequentially with other inactivated vaccines or live vaccines. LAIV4 may be administered simultaneously with other live or inactivated vaccines. However, after administration of a live vaccine (such as LAIV4), at least 4 weeks should elapse before another live vaccine is administered.

Influenza antiviral medications might reduce the effectiveness of LAIV4 if given within 48 hours before, to 14 days after administration of LAIV4. Persons who receive influenza antiviral medications within this period of LAIV4 vaccination can be revaccinated with another appropriate influenza vaccine (eg, IIV or RIV4).

TABLE 42-2

Comparison of Inactivated Influenza Vaccine (IIV) and Live-Attenuated Influenza Vaccine (LAIV)

Characteristic	IIV (IIV3/IIV4)	LAIV
Age groups approved for use	≥6 months	2–49 years
Immune status requirements	Immunocompetent or immunocompromised	Immunocompetent
Viral properties	Inactivated (killed) influenza A (H3N2), A (H1N1), and B viruses	Live-attenuated influenza A (H3N2), A (H1N1), and B viruses
Route of administration	Intramuscular	Intranasal
Immune system response	High serum IgG antibody response	Lower IgG response and high serum IgA mucosal response

POSTEXPOSURE PROPHYLAXIS

- Antiviral drugs available for prophylaxis of influenza should be considered adjuncts but are not replacements for annual vaccination.

- **Amantadine** and **rimantadine** are currently not recommended for prophylaxis or treatment in the United States because of the rapid emergence of resistance.
- The neuraminidase inhibitors **oseltamivir** and **zanamivir** are effective prophylactic agents against influenza in terms of preventing laboratory-confirmed influenza when used for seasonal prophylaxis and preventing influenza illness among persons exposed to a household contact who were diagnosed with influenza. **Table 42-3** gives dosing recommendations. **Peramivir** is not approved for chemoprophylaxis.
- In those patients who did not receive the influenza vaccination and are receiving an antiviral drug for prevention of disease during the influenza season, the medication should optimally be taken for the entire duration of influenza activity in the community.
- Prophylaxis should be considered during influenza season for the following groups of patients:

  ✔ Persons at high risk of serious illness and/or complications who cannot be vaccinated.

  ✔ Persons at high risk of serious illness and/or complications who are vaccinated after influenza activity has begun in their community because the development of sufficient antibody titers after vaccination takes ~2 weeks.

  ✔ Persons with severe immune deficiency or who may have an inadequate response to vaccination (eg, advanced human immunodeficiency virus [HIV] disease, persons receiving immunosuppressive medications), after exposure to an infectious person.

  ✔ Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution.
- LAIV should not be administered until 48 hours after influenza antiviral therapy has stopped, and influenza antiviral drugs should not be administered for 2 weeks after the administration of LAIV because the antiviral drugs inhibit influenza virus replication.
- Pregnant women, regardless of trimester, should receive annual influenza vaccination with IIV but not with LAIV.
- The adamantanes and neuraminidase inhibitors are not recommended during pregnancy because of concerns regarding the effects of the drugs on the fetus.
- Immunocompromised hosts should receive annual influenza vaccination with IIV but not LAIV.

TABLE 42-3

Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis—United States

Drug	Adult Treatment	Adult Prophylaxis[a]	Pediatric Treatment	Pediatric Prophylaxis[a]
CAP-dependent endonuclease inhibitor				
Baloxavirb[b,c]	12 years and older: 40–<80 kg: One 40 mg dose >80 kg: One 80 mg dose	None	FDA approved and recommended for use in children 12 years or older weighing at least 40 kg; see adult dosage	None
Neurominidase inhibitors				
Oseltamivir[d,e,f]	75-mg capsule twice daily × 5 days	75-mg capsule daily × 10 days	Term infants 0–8 months: 3 mg/kg/dose twice daily 9–11 months[g]: 3.5 mg/kg/dose twice daily or 3 mg/kg/dose twice daily ≥1 year: ≤15 kg: 30 mg twice daily >15–23 kg: 45 mg twice daily >23–40 kg: 60 mg twice daily >40 kg: 75 mg twice daily Duration: All for 5 days	Not recommended if <3 months 3–<12 months: 3 mg/kg/dose daily 9–11 months: 3.5 mg/kg/dose daily ≥1 year: ≤15 kg: 30 mg daily >15–23 kg: 45 mg daily >23–40 kg: 60 mg daily >40 kg: 75 mg daily Duration: All for 10 days
Zanamivir	10 mg (2 of 5 mg inhalations) twice daily × 5 days	10 mg (2 of 5 mg inhalations) daily × 10 days	10 mg (2 of 5 mg inhalations) twice daily × 5 days for ≥7 years old	10 mg (2 of 5 mg inhalations) daily for ≥5 years old × 10 days
Peramivir[c,e]	13 years and older: One 600 mg dose via intravenous infusion for 15–30 minutes	None	2–12 years of age: One 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for a minimum of 15–30 minutes	None

[a]If influenza vaccine is administered, prophylaxis can generally be stopped 14 days after vaccination for noninstitutionalized persons. When prophylaxis is being administered following an exposure, prophylaxis should be continued for 10 days after the last exposure. In persons at high risk for complications from influenza for whom vaccination is contraindicated or expected to be ineffective, chemoprophylaxis should be continued for the duration that influenza viruses are circulating in the community during influenza season.

[b]Time to peak = 4 hours. Food and cations (calcium, aluminum, magnesium, iron) can decrease peak concentration by 48%. Long half-life (79.1 hours) and is metabolized by UDP-glucuronosyltransferase (UGT1A3) and CYP3A4.

[c]For the treatment of uncomplicated influenza with oral baloxavir or intravenous peramivir, a single dose is recommended. Longer daily dosing (oral oseltamivir or intravenous peramivir) can be considered for patients who remain severely ill after 5 days of treatment.

[d]Oseltamivir dosing for preterm infants using their postmenstrual age (ie, gestational age + chronological age): <38 weeks: 1.0 mg/kg/dose twice daily; 38–40 weeks: 1.5 mg/kg/dose twice daily; >40 weeks: 3.0 mg/kg/dose twice daily.

[e]In patients with renal insufficiency, the dose should be adjusted on the basis of creatinine clearance. See https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

[f]Some experts recommend 150 mg twice daily for severe illness in pregnant women. Optimal dosing for prophylaxis in pregnant women is unknown.

[g]The American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily; CDC and US Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children aged 9–11 months.

Note: Although amantadine and rimantadine have been used historically for the treatment and prophylaxis of influenza A viruses, due to high resistance, the CDC no longer recommends the use of these agents for the treatment and/or prophylaxis of influenza.

TREATMENT

- Goals of Therapy: To shorten the duration of illness and provide symptom control.
- Antiviral drugs are most effective if started within 48 hours of the onset of illness. Adjunct agents, such as acetaminophen for fever or an antihistamine for rhinitis, may be used concomitantly with the antiviral drugs.
- Patients suffering from influenza should get adequate sleep and maintain a low level of activity. They should stay home from work and/or school in order to rest and prevent the spread of infection. Appropriate fluid intake should be maintained. Cough/throat lozenges, warm tea, or soup may help with symptom control (cough and sore throat).

Pharmacologic Therapy

- The neuraminidase inhibitors (**oseltamivir, zanamivir**, and **peramivir**) are the only antiviral drugs available for treatment and prophylaxis of influenza. Peramivir is the only intravenous formulation commercially available. The adamantanes (**amantadine** and **rimantadine**) are no longer recommended due to high resistance among influenza viruses.
- Oseltamivir, zanamivir, and peramivir have activity against both influenza A and influenza B viruses. When administered within 48 hours of the onset of illness, oseltamivir and zanamivir may reduce the duration of illness by ~1 day versus placebo. Benefits are highly dependent on the timing of initiation of treatment, ideally being within 12 hours of illness onset, up to 48 hours after onset of illness.
- Oseltamivir is approved for treatment in those older than 14 days, zanamivir is approved for treatment in those older than 7 years, and peramivir for those 18 years and older. The recommended dosages vary by agent and age (see **Table 42-3**), and the recommended duration of treatment for both agents is 5 days for oseltamivir and zanamivir and one dose for 1 day for peramivir.
- Neuropsychiatric complications consisting of delirium, seizures, hallucinations, and self-injury in pediatric patients have been reported following treatment with oseltamivir and peramivir.
- Oseltamivir and zanamivir have been used in pregnancy, but solid clinical safety data are lacking. Oseltamivir is preferred for the treatment of pregnant women because of its systemic activity; however, the drug of choice for chemoprophylaxis is not yet defined.
- Both the adamantanes and the neuraminidase inhibitors are excreted in breast milk and should be avoided by mothers who are breast-feeding their infants.

EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored daily for resolution of signs and symptoms associated with influenza, such as fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms will typically resolve within ~1 week. If the patient continues to exhibit signs and symptoms of illness beyond 10 days or a worsening of symptoms after 7 days, a physician visit is warranted, as this may be an indication of a secondary bacterial infection.

See Chapter 127, Influenza, authored by Jessica C. Njoku, for a more detailed discussion of this topic.